## Accumulation of a differentiation regulator specifies transit amplifying division number in an adult stem cell lineage.

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**Public Summary:**
In tissues that rapidly replace themselves, such as skin, intestinal epithelium, the male germline, and blood, a relatively few number of infrequently dividing adult stem cells are responsible for regenerating the designated tissue for the life of the organism. Adult stem cells divide asymmetrically to produce another stem cell and a differentiating daughter cell. In many systems, that differentiating daughter cell will go through many transit amplifying progenitor cell divisions before stopping division and becoming highly specialized mature cells. Transit amplifying progenitor cell divisions are important because they amplify cell number so that a small number of adult stem cells can maintain a great deal of differentiated tissue. Regulating the number of transit amplifying divisions is important because too few divisions could result in a paucity of mature tissue, while too many divisions may result in precancerous growth. We use fruit fly spermatogenesis to investigate how the number of transit amplifying divisions is regulated. We found through genetic perturbations and gene expression analyses that the rate of accumulation of a testis tumor suppressor protein determines the number of amplifying divisions. We also find that the interplay between the accumulation of the tumor suppressor protein and the rate of the cell cycle determine the final number of divisions. This study illuminates one regulatory strategy by which progenitor divisions may be counted in human stem cell lineages.

**Scientific Abstract:**
A key feature of many adult stem cell lineages is that stem cell daughters destined for differentiation undergo several transit amplifying (TA) divisions before initiating terminal differentiation, allowing few and infrequently dividing stem cells to produce many differentiated progeny. Although the number of progenitor divisions profoundly affects tissue (re)generation, and failure to control these divisions may contribute to cancer, the mechanisms that limit TA proliferation are not well understood. Here, we use a model stem cell lineage, the Drosophila male germ line, to investigate the mechanism that counts the number of TA divisions. The Drosophila Bag of Marbles (Bam) protein is required for male germ cells to cease spermatogonial TA divisions and initiate spermatocyte differentiation [McKearin DM, et al. (1990) Genes Dev 4:2242-2251]. Contrary to models involving dilution of a differentiation repressor, our results suggest that the switch from proliferation to terminal differentiation is triggered by accumulation of Bam protein to a critical threshold in TA cells and that the number of TA divisions is set by the timing of Bam accumulation with respect to the rate of cell cycle progression.

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